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● *Original Contribution*

CAROTID WALL ELASTOGRAPHY TO ASSESS MIDTERM VASCULAR DYSFUNCTION SECONDARY TO INTRAUTERINE GROWTH RESTRICTION: FEASIBILITY AND COMPARISON WITH STANDARDIZED INTIMA-MEDIA THICKNESS

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Abstract—Several studies have suggested that intrauterine growth restriction (IUGR) increases the risk of cardiovascular disease and early atherosclerosis. Early detection of arteriopathy is essential to early intervention. Although arterial intima-media thickness (IMT) is considered an index of subclinical atherosclerosis in the adult, its validity in pediatric patients may be limited. We have recently introduced a novel imaging-based biomarker (ImBioMark) to assess intrinsic mechanical features of the arterial wall from B-mode ultrasound data. The aim of the work described here was to evaluate the potential of ImBioMark in investigation of cardiovascular health status at the level of the common carotid artery (CCA) in adolescents born after IUGR. We also compared ImBioMark results with automated IMT measurements, a well-established biomarker used in clinical practice and research. The potential sequelae of IUGR on the CCA were examined in a group of adolescents in comparison with healthy controls. Patients with IUGR (n = 7) were 13.85 ± 0.46 y old; the healthy controls (n = 7) were 14.58 ± 0.80 y old ($p = 0.058$). Cine loops of the CCA B-mode data were digitally recorded, and the arterial elastic modulus was estimated *a posteriori* with ImBioMark. IMT of the CCA was automatically calculated using QLAB software (Philips, Andover, MA, USA). All patients had been evaluated *in utero* in our fetal echocardiographic laboratory. ImBioMark detected a significant increase in CCA stiffness in patients with IUGR as compared with healthy controls: elastic modulus = 90.74 ± 11.86 versus 61.30 ± 15.94 kPa, respectively ($p = 0.002$). There was, however, no significant difference between patients with IUGR and controls in IMT (0.483 ± 0.067 versus 0.476 ± 0.051 mm, respectively, $p = 0.831$). The impact of IUGR on CCA wall dynamics was confirmed by ImBioMark. The apparent limitation of IMT measurement in this cohort may be the result of geometric arterial changes, that is, the expected thickening, below the level of detection at this age. As early detection of vascular modulation is essential to early intervention in a population at risk, we now intend to extend ImBioMark to investigate larger pathologic cohorts with various degrees of arteriopathy. (E-mail: roch.maurice@creatis.insa-lyon.fr or roch.maurice.hsj@ssss.gouv.qc.ca) **Crown Copyright © 2014 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Intrauterine growth restriction, Arteriopathy, Atherosclerosis, Intima-media thickness, Carotid elasticity, Ultrasound elastography.**

INTRODUCTION

It is now known that intrauterine growth restriction (IUGR) increases the risk of cardiovascular disease and early atherosclerosis. Indeed, several epidemiologic investigations have revealed an inverse relationship between birth weight and later systemic hypertension (Jarvelin et al. 2004; Law et al. 2002; Loos et al. 2001), coronary artery disease and cerebrovascular accidents (Kaijser et al. 2008). However, there are no studies correlating findings on fetal circulation with pediatric or/and pre- to early-adult cardiovascular function.

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Intima-media thickness (IMT) is a widely used non-invasive ultrasound-based biomarker of subclinical atherosclerosis in adult (Lorenz et al. 2007) and pediatric (Thijssen et al. 2010; Urbina et al. 2009a) populations. Increased IMT has been reported in pediatric populations with, namely, familial hypercholesterolemia (Aggoun et al. 2000; Lavrencic et al. 1996), hypertension (Sorof et al. 2003; Urbina et al. 2011), type 1 diabetes (Frost and Beischer 2003; Järvisalo et al. 2002), obesity (Ozcetin et al. 2012; Urbina et al. 2009b) and metabolic syndrome (Iannuzzi et al. 2006).

Our group derived the theoretical framework for the "non-invasive vascular elastography" method (Maurice et al. 2004), which was validated on vessel-mimicking phantoms (Maurice et al. 2005) and applied in clinical studies (Maurice et al. 2008). Although radiofrequency data were used in previous applications, non-invasive vascular elastography was also adapted to process B-mode images; it was referred to as *ImBioMark* (imaging-based biomarker) (Maurice et al. 2012). By use of an optical flow-based algorithm, ImBioMark was very recently adapted to investigate aortic wall remodeling in a pediatric population afflicted with Kawasaki disease, an illness causing acutely acquired vasculitis during early childhood (Maurice and Dahdah 2012). This method has the advantage of being compatible with typical B-mode data under a DICOM format for archiving, which is convenient for widespread applicability.

In this work, we evaluated the potential of ImBioMark to investigate the sequelae of IUGR on the common carotid artery (CCA) during adolescence. CCA elastic moduli were computed for the IUGR population and were compared with values of normal controls to quantify CCA stiffness. We also introduced an automated geometry-based elastic modulus calculation method. ImBioMark results were then compared with automated IMT measurements, as well as geometry-based measurements of the CCA, and with the fetal circulatory status of study patients.

METHODS

Populations investigated

We compared adolescents born after IUGR (n = 7, 13.85 ± 0.46 y old) with normal controls (n = 7, 14.58 ± 0.80 y), matched for age ($p = 0.058$). All 14 patients had been evaluated *in utero* in our fetal echocardiography laboratory. The study patients were referred to the fetal cardiac unit for IUGR. The controls were referred to the fetal cardiology clinic for a previous familial history of congenital heart disease. The IUGR group was selected on the basis of two main criteria: (i) detection of abnormal flow in the uterine and/or umbilical arteries during fetal evaluation (Chan et al. 1995); (ii) fetal growth retardation (below the third percentile for gestational age at birth) according to Canadian birth weight charts (Kramer et al. 2001). Other essential data such as birth weight, height and cranial circumference were also recorded. Study patients were called back for evaluation at ages 13 to 15 y according to a standardized protocol. With the exception of IUGR status, all patients included in this study were free of known cardiovascular comorbidities or known cardiovascular risk factors. Cardiovascular ultrasound, blood pressure, weight and height were accordingly obtained. IMT, ImBioMark and geometry-based mechanical parameters were computed *a posteriori*, as further described below. The institutional ethics committee approved the study, and written informed consent was obtained from the patients' parents for this investigation.

Vascular ultrasound data acquisition

B-Mode data of longitudinal segments of the right CCA were recorded with an iE33 (Philips, Andover, MA, USA) echography machine, using an 11-MHz probe. The frame rate was generally close to 40 Hz depending on the depth, which was typically 4 cm with the focus positioned in the middle of the CCA. Three loops of seven to eight beats were recorded serially. We then analyzed four to five complete consecutive cardiac cycles. Finally, for each subject, data from the three recorded loops were averaged. Blood pressure was measured with an automated sphygmomanometer (Welch Allyn, Skaneateles Falls, NY, USA) at the beginning of imaging recording. Electrocardiographic signals were simultaneously recorded for appropriate cardiac cycle determination, as well as proper identification of systole and diastole.

Measurement of intima-media thickness

The CCA IMT was automatically computed with QLAB software (Philips). As illustrated in the B-mode image of a control's CCA in Figure 1(a), the intima-media layer is characterized by an echogenic surface that lies between the blood and the adventitia. After manual selection of a region of interest (ROI, typically 1 cm) that included the far wall, the intima-media was automatically segmented, and the IMT computed. On the basis of electrocardiographic tracking, the IMT was calculated in late diastole. The final IMT values were averages of five measurements.

ImBioMark elastic modulus calculation (E_{IBM})

The ImBioMark results reported for this study were averaged from the three recorded data sets of each CCA. As previously described in the literature (Maurice and Dahdah 2012; Maurice et al. 2012; Zakaria et al. 2010), ImBioMark allows appropriate assessment of arterial

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